



Association between allergic diseases and attention deficit hyperactivity disorder in childhood

Çocukluk çağında allerjik hastalıklar ile dikkat eksikliği ve hiperaktivite bozukluğu arasındaki ilişki

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ABSTRACT

Objective: Attention Deficit Hyperactivity Disorder (ADHD) is a common childhood problem similar to allergic disorders. The aim of the study is to determine whether allergic disorders and atopy are associated with physician-diagnosed ADHD.

Materials and Methods: This study was designed as a nested case-control study. One hundred sixty children were divided into three groups; 55 patients with ADHD, 55 children of healthy siblings of the study group and 50 unrelated healthy children. For each subject, an International Study of Asthma and Allergies in Children (ISAAC) questionnaire was completed. The total eosinophil count, total IgE levels were measured and skin prick tests were performed.

Results: The prevalence of asthma was significantly higher in the ADHD group than the control group but was similar to the sibling group. Even though prevalence of rhinitis was significantly higher in ADHD group relative to the other groups, atopic rhinitis was similar in all groups. There were no significant differences for prevalence of eczema, elevated total IgE levels, eosinophil count and positive skin prick testing between any of the groups.

Conclusion: The rhinitis seems to be a risk factor for ADHD while atopic status does not appear to be involved. Nasal obstruction and sleep disturbances due to rhinitis may affect the cognitive functions of individuals with ADHD. These individuals should be evaluated to determine whether or not (allergic) rhinitis accompanies ADHD.

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Key words: Asthma, allergy, attention deficit hyperactivity disorder, rhinitis

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ÖZ

Giriş: Dikkat eksikliği ve hiperaktivite bozukluğu (DEHB) çocukluk çağında allerjik hastalıklarda olduğu gibi sık karşılaşılan bir problemidir. Bu araştırmanın amacı doktor tanılı DEHB ile allerjik hastalık ve atopi arasındaki ilişkinin belirlenmesi amaçlandı.

Gereç ve Yöntem: Bu araştırma olgu-kontrol çalışması olarak planlanmıştır. Araştırmaya dahil edilen 160 çocuk üç gruba ayrıldı. Çalışma grubunu DEHB tanısı alan 55 çocuk, ikinci grubu çalışma grubunda bulunan çocukların kardeşleri (n= 55), kontrol grubunu ise sağlıklı 50 çocuk oluşturdu. Tüm çocuklara, Çocuklarda Uluslararası Astım ve Allerji Çalışması (ISAAC) anket formu uygulandı. Kanda toplam eozinofil sayısı, serum IgE düzeyi ölçüldü ve cilt prick testi uygulandı.

Bulgular: Astım sıklığı, DEHB grubunda kardeşleriyle benzer ancak kontrol grubuna göre anlamlı düzeyde yüksek çıktı. Rinit sıklığı DEHB grubunda diğer iki gruba göre daha yüksek çıkarken, gruplar arasında atopik rinit sıklığı benzerdi. Egzama sıklığı, toplam IgE ve eozinofil düzeyleri ve cilt prick testi pozitifliği açısından gruplar arasında farklılık belirlenmedi.

Sonuç: Atopi her ne kadar etkili olmasa da rinit DEHB için risk faktörü olarak görülmektedir. DEHB'li kişilerde rinite bağlı burun tıkanıklığı ve uyku bozukluğu bilişsel fonksiyonları etkileyebilir. Bu kişilerde allerjik olsun ya da olmasın DEHB'ye rinit eşlik edip etmediği belirlenmelidir.

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Anahtar kelimeler: Astım, allerji, dikkat eksikliği ve hiperaktivite bozukluğu, rinit

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INTRODUCTION

Allergic diseases affect a large percentage of the pediatric population^[1,2]. These disorders, especially rhinitis may cause sleep disturbances, poor school performance, hyperactivity, decreased quality of life, cognitive difficulties, irritability, behavioral problems and mood disorders^[3,4].

Attention Deficit Hyperactivity Disorder (ADHD) is also a common chronic neuropsychiatric disease in childhood with an estimated prevalence of 12.9%. Its characteristic features are difficulties with attention, impulsivity and hyperactivity^[5]. Even though the genetic, environmental, hematologic, and endocrinologic factors are accused, the etiology of ADHD is not still well-known clearly^[6].

The co-occurrence of psychiatric symptoms and allergies has intrigued clinicians and researchers for more than 80 years. To date data concerning the causal association between ADHD and allergic disorders are conflicting^[7,8]. After then several studies have provided that there is an association between allergic disorders and ADHD^[9-11]. Beyreiss and Roth planned two controlled studies in populations of atopic children and found that ADHD and allergic disorders are linked^[12,13]. In contrast, the findings of other two different studies investigated atopic and non-atopic children in terms of ADHD and they concluded that there was no association between these two conditions.

Even though ISAAC questionnaire is suggested to screen allergic disorders such as allergic rhinitis, asthma and eczema, skin prick test and/or serum specific IgE levels must be performed to confirm allergic pathogenesis^[14].

The primary goal of our study was to investigate the relationships between allergic disorders and atopy with ADHD as discussed recently^[7,9-12]. First, we tested the hypothesis that rates of allergic diseases and allergen sensitivity would be elevated among children with ADHD. Second, in addition to control group we also evaluated the siblings of patients with ADHD and in this way we aimed to minimize genetic and environmental factors which affect the pathogenesis of both atopic disorders and ADHD.

MATERIALS and METHODS

This study was designed as a nested case-control study. Children, aged 7 to 12, with child psychiatrist-diagnosed ADHD who met Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV) criteria for ADHD were referred to the allergist for the assessment of the possibility of atopic disorders^[15]. The patients with systemic disease without atopic disorders were excluded.

Two different control groups were formed. First group consisted of siblings of ADHD patients. If the patient has more than one sibling, age of the closest sibling was invited to evaluate atopy, ISAAC questionnaire, and DSM IV criteria. Patients without sibling or with sibling diagnosed as having ADHD were excluded. The patients and control group with systemic disease without atopic disorders were excluded.

The second control group consisted of unrelated children. These children were selected among cases who admit outpatient clinic to check their health status without any complaint.

After informed consent was obtained, subjects were screened for atopic diseases with a focused history and ISAAC questionnaire, focused physical examination, total IgE levels, total eosinophil count and skin prick testing^[16]. The same allergist performed the history and physical examination.

The allergist interviewed the parent regarding any history of asthma, wheezing, eczema, urticaria and rhinitis. These questions were asked in ISAAC questionnaire: for asthma - "Have you had wheezing or whistling in the chest in the last 12 months?" and for atopic rhinoconjunctivitis - "In the past 12 months, have you had a problem with sneezing or a runny or a blocked nose when you did not have a cold or the flu? If yes: in the past 12 months, has this nose problem been accompanied by itchy-watery eyes?" for atopic eczema - "Have you ever had an itchy rash which was coming and going for at least 6 months? If yes: Have you had this itchy rash at any time in the last 12 months? If yes: Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?" The validity of the translation has been confirmed in previous studies in Turkey^[12].

Socio-demographic features, positive atopic family history, living in urban or rural area, passive smoking, number of person living in the house, duration of breastfeeding and feeding with formula, delivery way, birth weight were questioned.

Children were asked to supply a blood sample which was assayed for total serum IgE and eosinophil count. Skin prick testing was performed for common inhaler allergens *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Aspergillus fumigatus*, *Alternaria alternata*, cat and dog rander, ragweed, tree pollens (*Ulmus*, *Quercus*, *Populus*, *Platanus*, *Salix*) and certain grass pollens (*poa mix*, *C. dactylon*, *P. pratensis*, *D. glomerata*, *A. sativa*, *Festuca*) (Laboratoire des Stallergenes, Fresnes Cedex, France) with a response considered positive if

the wheal was at least 3 mm greater than the negative control^[17].

Asthma was defined as asthma diagnosed by a doctor or a diagnosis of allergic bronchitis and/or ≥ 3 bronchitis episodes, and wheezing or whistling in the chest or asthma crisis in the last 12 months. Rhinitis was based on a positive to questions about having had a problem with sneezing, or a runny or blocked nose during last 12 months when the child did not have a common cold or flu. If the patient has rhinitis and at least one positive skin prick testing, it was named as allergic rhinitis. Eczema was defined as recurrent erythema, and itching or rash on the body without fever in the last six months^[2,18].

All subjects and their families were informed about the study and procedures and were signed the informed consent. The study protocol was approved by Ondokuz Mayıs University Ethics Committee.

Statistical Analysis

Analysis of the data was performed using the Statistical Package for the Social Sciences for Windows (SPSS 18.0) program. The association between groups and the other characteristics were found by Chi-square analysis. The comparisons of groups were done by Mann-Whitney U-test and Kruskal-Wallis analysis for non-normal continuous variables; student t test and ANOVA analysis for normal continuous variables. Mean values were obtained along with their standard deviations (mean \pm SD). Multinomial logistic regression analysis was used for obtaining corrected odds ratios (OR) for sex and passive smoking. P values below 0.05 were considered statistically significant in all analyses and confidence interval (CI) was accepted as 95%.

RESULTS

Eighty two patients were diagnosed as ADHD in the study period. Ten patients were excluded because they had no siblings. Three patients were excluded because their siblings have systemic diseases. Fourteen patients did not want to participate in the study. At the end we assessed 55 ADHD patients, their 55 siblings and 59 healthy children.

The age, positive atopic familial history, living in urban or rural area, duration of breastfeeding, smoking in pregnancy, passive smoking, delivery way, birth weight did not meaningfully differ between the groups. These characteristics of the subjects were shown in Table 1. Forty-six of patients were male and 9 patients were female in the study group. Male/female ratio of the sibling's group was 33/22 and 35/24 in control group. There was a statistical difference between two control groups and the study group. In multivariate analysis it was seen that this sex difference did not affect the prevalence of asthma

($p=0.60$, OR: 0.78; 95% CI: 0.30-1.99) and rhinitis ($p=0.94$, OR: 1.04; 95% CI: 0.37-2.94). No differences were seen between the groups for eczema. The prevalence of symptoms associated with atopy and asthma in the groups was summarized in Table 2 and 3. The results of eosinophil count, having elevated IgE and skin prick testing were summarized in Table 4. The differences between groups were not statistically significant.

DISCUSSION

Since specific biologic and psychosocial risk factors are critical to the development of prophylaxis and treatment of individuals with ADHD, there have been many researchers have studied co-morbidities of ADHD^[19]. Many years ago, Frederic Speer observed that children with allergies had exaggerated and accelerated motor function, a tendency toward hyperactivity, heightened irritability and excitability and short attention spans. He also observed that they had poorly developed motor skills compared to their peers without allergies^[20]. Subsequently, many studies were conducted to investigate the relationship between allergic disorders and ADHD^[4,8-11,21]. However, based on the results of research reported in the medical literature, a clear association has not been established between ADHD and atopic disorders.

In this study, the prevalence of allergic sensitization among the ADHD patients was 30.9% consistent with a previous study reporting 35.2% whereas lower than a previous study which reported 67.5%^[22,23]. In the last report, they could have found high prevalence of allergic sensitization due to the fact that most of the study population lived in urban areas^[23]. Our result was also similar with both siblings and control group.

It was known that boys have an increased risk for ADHD compared with girls, with a ratio of approximately 3.5 to 1^[5]. We also found that ADHD is more frequent in males with a ratio of approximately 5 to 1. Therefore we used adjusted results for gender differences in groups.

While explaining the association between allergy and ADHD, it was hypothesized that allergic reactions engender cholinergic-adrenergic activity imbalances in the central nervous system, leading to poorly regulated arousal levels and ADHD behaviors in some children^[24]. After that Brawley et al. thought that allergic rhinitis could play a role in the behaviors associated with ADHD^[21]. Brawley evaluated the prevalence of allergic rhinitis in 30 patients with ADHD and concluded that 80% had symptoms of rhinitis, 61% had at least one positive skin prick testing, 53% had other atopic disorders and 100% had a positive atopic familial history. Moreover, they observed that none of their ADHD patients had

Table 1. Characteristics of the subjects

	Patients (n= 55)	Siblings (n= 55)	Control (n= 50)	p
Age (year) (mean ± SD)	10.1 ± 2.3	9.7 ± 4.5	8.1 ± 3.5	NS
Male sex (%)	83.6	60	52	0.002*
Birth weight (g) (mean ± SD)	3282 ± 556	3192 ± 509	3295 ± 626	NS
Vaginal delivery (%)	74.5	69.0	58.0	NS
Breast feeding (month) (mean ± SD)	10.5 ± 6.9	9.3 ± 6.4	11.1 ± 8.9	NS
Passive smoking (%)	60.0	60.0	21.4	0.02**
Smoking in pregnancy (%)	14.5	14.5	8	NS
Familial atopy (%)	23.6	23.6	14	NS
Living in urban area (%)	78.2	78.2	74	NS

SD: Standard deviation, NS: Non-significant.

* The difference is between patients group and the other groups.

** The difference is between control group and the other groups.

Table 2. The evaluation of the atopic symptoms and diseases in the groups

	Patients n (%)	Siblings n (%)	Control n (%)	p
Wheezing in any time in the life	17 (30.9)	13 (23.6)	6 (12.0)	NS
Wheezing in last year	13 (23.6)	7 (12.7)	5 (10.0)	NS
Rhinitis	25 (45.5)	11 (20.0)	8 (16.0)	0.005*
Rhinitis (with atopy) [#]	8 (14.5)	5 (9.1)	4 (8)	NS
Asthma	15 (27.3)	8 (14.5)	4 (8.0)	0.03**
Eczema	2 (3.6)	1 (1.81)	2 (4.0)	NS

NS: Non-significant.

* The difference is between patients group and the other groups.

** The difference is between patient group and control group.

At least one positive skin prick test result for common inhaler allergens.

Table 3. Corrected results of subjects for sex and passive smoking

	ADHD			
	Siblings		Control	
	*OR (95% CI)	p	*OR (95% CI)	p
Asthma	2.06 (0.7-5.63)	0.16	2.93 (0.82-10.47)	0.09
Rhinitis	4.61 (1.81-11.73)	0.001	4.71 (1.71-12.94)	0.003
Rhinitis (with atopy)**	1.81 (0.52-6.31)	0.35	1.93 (0.49-7.55)	0.35
Atopy	1.56 (0.62-3.93)	0.34	2.89 (0.99-8.42)	0.51

* Corrected odds ratios for sex and passive smoking.

** At least one positive skin prick test result for common inhaler allergens.

Table 4. The laboratory evaluation of the groups

	Patients (n= 55)	Siblings (n= 55)	Control (n= 50)	p
Subjects with elevated IgE* n (%)	16 (29.1)	9 (16.4)	12 (24.0)	NS
Eosinophil count/mL [median (min-max)]	200 (10-1500)	200 (0-1900)	100 (0-700)	NS
Positive skin prick testing n (%)	17 (30.9)	11 (20)	7 (14)	NS

NS: Non-significant, SD: Standard deviation.

* IgE > 100 IU/mL.

been previously diagnosed with allergic rhinitis^[21]. The prevalence of rhinitis (other than cold or flu) in children is 11.0-38.8% in Turkey^[3,25]. This prevalence is similar in our two control groups. Interestingly, in our study, we saw that the most important factor associated with ADHD was rhinitis and 72.7% of them were newly diagnosed.

Mitchell et al. did not find differences in the rates of allergic diseases among 48 hyperactive children when compared with 49 matched controls^[26]. McGee and colleagues followed 1037 children ranging in age from 3 to 18 years and assessed symptoms of ADHD and other psychiatric symptoms and measures of atopy but did not find an association between ADHD symptoms and clinical and biologic measures of atopy^[27]. Blank and Remschmidt also did not find any differences in IgE mediated reactions between children with ADHD and a control group^[28].

Schmitt et al. reviewed the relationship between atopic disorders and ADHD^[29]. They evaluated twenty studies and emphasized that most studies relied on parental reports to define presence or absence of atopic disorders. Our study is important because of using skin prick test to diagnose atopy. There is no doubt that all of asthma, rhinitis and eczema do not develop with atopic march. It can be hypothesized that the relationship between ADHD and asthma, rhinitis and eczema may be independent of atopy and parental reports may be misleading. It was shown that reducing the nasal congestion independent of allergy resulted in decreased sleep disturbances and daytime somnolence^[20]. Because the prevalence of allergic diseases without rhinitis and positive skin prick testing are similar in individuals with ADHD and their siblings, we concluded that individuals with ADHD may be especially affected by rhinitis without atopy. We thought that rhinitis may have an important role to trigger symptoms of ADHD, while atopy, asthma, allergic rhinitis or eczema do not. Schmitt and Romanos also draw attention a research gap concerning the association between ADHD and allergic disorders^[29]. They indicated that sleep disturbances leads to daytime fatigue, mood changes and impaired psychosocial functioning and may resemble and/or exacerbate ADHD^[30,31]. Recently, Tsai et al. reported a population based study and revealed an increased rate of ADHD among children with allergic rhinitis^[11]. We speculate that symptoms of rhinitis, independent of atopy, may lead to inattention and impulsivity because of sleep deprivation. It is also known that genetic and environmental factors affect the occurrence of both allergic diseases and ADHD^[6,32]. We saw that the only significant difference between ADHD patients and their

siblings was rhinitis. We would like to emphasize that rhinitis, independent of allergy, per se may have an important role in ADHD. We concluded that individuals with ADHD symptoms should be evaluated specifically for the presence of rhinitis.

Some limitations of this study should be noted. The diagnosis of allergic diseases was especially based on parental and self-reporting according to ISAAC questionnaire. We conclude that the use of parental reporting may unlikely cause to lead to substantial under- or over-reporting of disease severity and prevalence. There is a bias between the prevalence of rhinitis symptoms that was reported as %38.8 for Samsun and control groups^[2]. This significant difference maybe a reason of the selected cases referred to the university hospitals. Nevertheless, the true prevalence of the allergic rhinitis has not been reported yet. This study was a cross-sectional survey, therefore it is not possible to observe the effects on allergic diseases and psychological and behavioural problems. It could be demonstrated the results by the treatment of allergic rhinitis on ADHD.

In conclusion our data show that frequency of non-atopic rhinitis is increased in children with ADHD. There were no relationships between atopic disorders and ADHD. Further studies which investigate whether the evaluation and treatment of rhinitis reduce symptoms of ADHD are needed to understand the impact of rhinitis on ADHD.

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